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# $\beta$-Lactam-4-ylidenes

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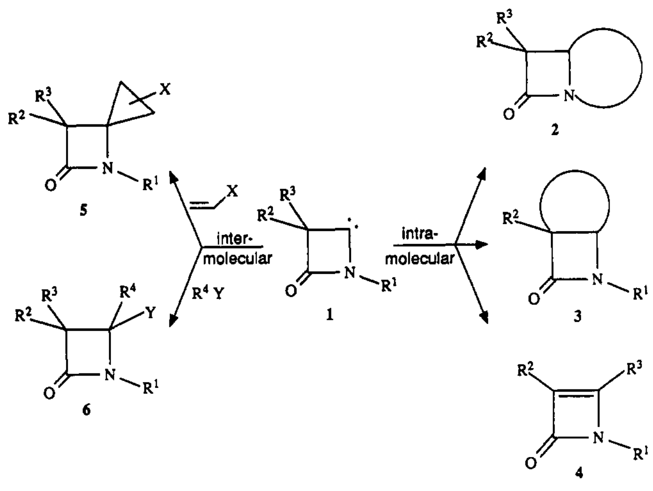
*Summary:* $\beta$-Lactam-4-ylidenes, generated by thermolysis of easily accessible spiro-fused $\beta$-lactam oxadiazolines, are trapped in typical intramolecular and intermolecular carbene reactions.

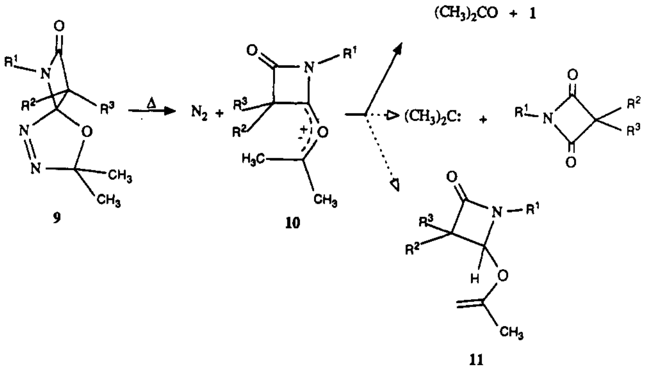
Despite intense activity in the area of $\beta$-lactam chemistry since 1943,[1] there is still much interest in synthetic methods for the elaboration of relatively simple $\beta$-lactams into more complex structures. In principle a $\beta$-lactam with a carbene center at C-4 (**1**) could provide the means for extending $\beta$-lactams with suitable substituents at N-1 and C-3 in the five general directions of Scheme I. That is, intramolecular ring closures leading to bicyclic products **2** and **3** might be developed with built-in carbene-scavenging functional groups in $R^1$ or $R^3$. Alternatively, carbene rearrangement (1,2-migration) could lead to azetinone[2] intermediates (**4**), which might be elaborated by means of intermolecular or intramolecular Michael addition, for example. Finally intermolecular capture of **1** by cycloaddition to alkene (or alkyne) moieties, or by insertion reactions, could lead to **5** and **6**, respectively. In spite of the potential of $\beta$-lactam-4-ylidenes as synthetic intermediates, they have not been reported. Corresponding $\beta$-lactam-3-ylidenes are also unknown, although 3-diazo-$\beta$-lactams[3] have served as carbene equivalents.

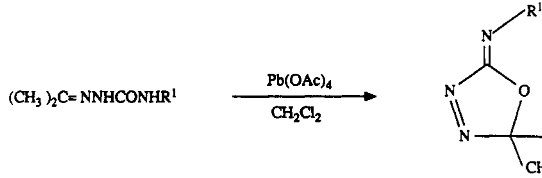
We report the synthesis of nine members of the 1,7,8-triaza-5-oxa-2-oxospiro[3,4]oct-7-ene family (**9**) and evidence that they undergo thermal decomposition in solution to afford carbenes **1**.

**Scheme I**



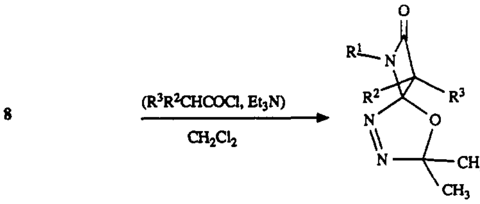
**Scheme II**





7 8 [1]

2-Imino-$\Delta^3$-1,3,4-oxadiazolines (**8**) were prepared[4] by oxidative cyclization of 4-substituted semicarbazones of acetone (**7**, eq 1). Like imidates[5] and 2-imino-$\Delta^3$-1,3,4-thiadiazolines,[6] **8** are converted to $\beta$-lactam systems upon treatment with acid chlorides and triethylamine.[7] In a typical reaction, the acid chloride (3.0 mmol) in dry methylene chloride (10 mL) was added in ca. 30 min, with stirring, to a solution of **8** (2.5 mmol) and triethylamine (6.0 mmol) in methylene chloride (20 mL) at ca. −23 °C. After overnight stirring at ambient temperature the mixture was worked up to afford **9**, eq 2, in yields ranging from



[2]

9

**9a**: $R^1 = R^2 = R^3 = Ph$; **b**: $R^1 = Ph$, $R^2 = R^3 = Me$; **c**: $R^1 = Me$, $R^2 = R^3 = Ph$; **d**: $R^1 = CH_2Ph$, $R^2 = R^3 = Ph$; **e**: $R^1 = R^2 = R^3 = Me$; **f**: $R^1 = p\text{-}C_6H_4OMe$, $R^2 = R^3 = Cl$; **g**: $R^1 = p\text{-}C_6H_4OMe$, $R^2 = R^3 = Me$; **h**: $R^1 = Ph$, $R^2 = H\ (OPh)$, $R^3 = OPh\ (H)$, one diastereomer of unknown configuration; **i**: $R^1 = CH_2CH_2OSi(CH_3)_2C(CH_3)_3$, $R^2 = R^3 = Ph$; **j**: $R^1 = CH_2CH_2OH$, $R^2 = R^3 = Ph$.

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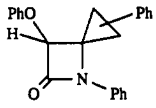
60 to 98%. Compounds **9a–i**, as well as **9j** ($R^1 = CH_2CH_2OH$, $R^2 = R^3 = Ph$), obtained by desilylation of **9i** with $F^-$, were purified by chromatography, and they were identified by $^{13}C$ and $^1H$ NMR spectroscopy, infrared spectroscopy, and CI mass spectroscopy. Those spectra firmly identified the spiro-fused skeleton of **9** in all of them because the structure of **9a** was confirmed by single-crystal X-ray diffraction.

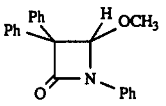
Thermolysis of **9a–d** as solutions (~0.2 M) in benzene (sealed tube) were first-order with $k_1 = (1.0\text{–}2.8) \times 10^{-4}\ s^{-1}$ at 100 °C. In each case the yield of acetone was 95% or greater ($^1H$ NMR, internal toluene reference), implying that cycloreversion to $N_2$ and a carbonyl ylide[8] is followed by clean, unidirectional fragmentation of the ylide[9-11] (Scheme II). Competition from the alternative sense of ylide fragmentation was not noticeable[12] nor were ring closure to oxirane (not shown) or 1,4-sigmatropic rearrangement to **11** detected.[13] It follows that fragmentation to **1** is fast relative to the other potential, unimolecular competing processes of the ylide that could lower the yields of **1**.

Presumably **1** is stabilized by delocalization of the N-electrons ($R\ddot{N}{-}\ddot{C}{-} \leftrightarrow R\overset{+}{N}{=}\ddot{C}{-}$) but the contribution of the dipolar structure must be small, given that the carbonyl group decreases the basicity of the lactam nitrogen and taking into account the fact that a diaminocarbene[14] has only a small negative charge (0.08 e) on the carbene carbon.

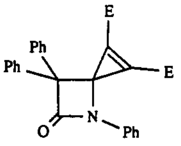
Support for the mechanism of Scheme II is based on the following carbene trapping experiments carried out in sealed tubes. Thermolysis of **9h** in styrene afforded **12**[15] in 74% yield (major of two isomers 62%) with or without added rhodium(II) acetate[16] dimer. Thermolysis of **9a** in benzene afforded **13** (100%) with methanol (12.0 M) added[17] and **14** (33%) in the presence of dimethyl acetylenedicarboxylate (2.0 M).[18] Thermolysis of **9j** in benzene gave the expected oxapenam **15** (50%).[18] These results are very promising and additional work designed to test for the other potential applications of β-lactam-4-ylidenes (Scheme I) is in progress.



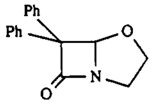
**12**



**13**



**14**, $E=CO_2CH_3$



**15**

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[9] Preferred fragmentation of carbonyl ylides bearing an amino substituent, in the sense that would lead to amino carbene, was predicted from theory.[10] It is unlikely that the amido nitrogen in **10** is the sole cause for the highly selective fragmentation because alkoxy substituents are not sufficient to promote clean fragmentation of carbonyl ylides to alkoxycarbenes.[8c,11]

[10] Houk, K. N.; Rondan, N. S.; Santiago, C.; Gallow, C. J.; Gandour, R. W.; Griffin, G. W. *J. Am. Chem. Soc.* **1980**, *102*, 1504.

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[12] Propene, from rearrangement of 2-propanylidene, was not detectable by $^1H$ NMR spectroscopy. An upper limit on the propene yield is imposed by the high yield of acetone in any case.

[13] Sigmatropic rearrangement products such as **11** are readily detected in the $^1H$ NMR spectrum.[8f]

[14] Arduengo, A. J. III.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

[15] One other example with the skeleton **12** is known, but the approach was totally different. de Meijere, A.; Teichmann, S.; Yu, D.; Kopf, J.; Oly, M.; von Thienen, N. *Tetrahedron* **1989**, *45*, 2957.

[16] Rhodium(II) acetate dimer would affect the outcome if a diazo intermediate were involved because it converts such intermediates to carbenoids. Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

[17] The quantitative yield of **13** implies that ylide fragmentation is fast or that ylide quenching by methanol is slow. Rate constants for unimolecular and bimolecular reactions of carbonyl ylides are very dependent on substituents. Methanol traps some carbonyl ylides efficiently but it failed to quench the ylide formed by attack of fluorenylidene on aliphatic ketones. Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6631.

[18] Structure confirmed by single-crystal X-ray diffraction. We are indebted to Dr. Chris Frampton for the X-ray work on both **9a** and **14**. The structure of **12**, and **13**, and **15** were anchored to that of **14** through infrared and $^{13}C$ NMR spectra. Those correlations were supported with high-resolution mass spectra for **13** and **15**.